

USE OF STREPTOMYCIN IN THE TREATMENT AND CONTROL OF  
TUBERCULOSIS IN JAPAN

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1. INTRODUCTION

Tuberculosis is the number one public health problem in Japan today. It is also an important consideration in the economic rehabilitation of the Nation. The magnitude of the tuberculosis problem in Japan is well recognized and vigorous effort toward its control are being exerted. For example, as many hospital beds as possible are being rehabilitated and made available; extra rations have been made available to all tuberculosis patients in hospitals; health centers have been reorganized with special emphasis on tuberculosis control; personnel are being trained in clinical and public health control techniques; an extensive BCG vaccination program is being undertaken, and; a high protein diet is being provided for school children through the school lunch program. These are all important steps and constitute major contributions to the solution of this problem, however, they are, in themselves, inadequate and a maximum effort is imperative.

Within the past few years streptomycin has been developed and tested in the United States and has been found, after extensive tests, to be very effective in the treatment of certain types of tuberculosis, particularly early lesions which are still soft and vascular.

Japan is still faced with hundreds of thousands of persons already affected with tuberculosis, many of whom can be saved from death and returned to usefulness if properly treated. Streptomycin which is being introduced into Japan at this time offers hope for many of these cases. The introduction of streptomycin marks another major contribution to the tuberculosis control program in Japan.

In December 1948 a culture of streptomycin griseus was obtained from Rutgers University and turned over to officials of the National Institute of Health for development and distribution to manufacturing laboratories as the first step toward commercial production. There will, of necessity, be a time lag before locally produced streptomycin will be available, but it is not possible at this time to determine how long this period will be. In order to bridge this gap and make streptomycin immediately available for the treatment of early cases of tuberculosis arrangements were made to import 200,000 grams from the United States. This imported streptomycin, which will arrive in Japan on or about 1 April 1949 will be distributed by the Ministry of Welfare for use in qualified hospitals only.



The plan of distribution will take into consideration the annual number of tuberculosis deaths in each prefecture; hospital facilities available; and, the availability of qualified technical personnel to supervise streptomycin therapy. Each qualified hospital will be permitted to procure its fair share of the drug in accordance with this plan. The Ministry of Welfare will issue appropriate instructions to all prefectural health departments, national hospitals, tuberculosis sanatoria and other agencies concerned.

The decision to use streptomycin in the treatment of all early cases of tuberculosis has been influenced by the need for a rapid turnover of hospital beds in the various institutions treating tuberculosis. The use of streptomycin will shorten the hospital stay and permit more effective utilization of hospital beds. This will alleviate, to a certain extent, the shortage of tuberculosis hospital beds, which is at present one of the important deficiencies in the tuberculosis control program.

## 2. STREPTOMYCIN IN THE TREATMENT OF HUMAN TUBERCULOSIS.

The deficiency of information and experience in Japan concerning the indications and use of streptomycin has necessitated the preparation and distribution of information with respect to its use in the treatment of tuberculosis. In view of this fact an article containing a review of the American literature has been prepared by this Section and translated into Japanese. It will shortly appear in the Journal of the Japan Medical Association. The Ministry of Welfare is using the same translation to disseminate the information to all those responsible for tuberculosis control.

Subject article entitled "Streptomycin in the Treatment of Human Tuberculosis" is reproduced herein (Incl. #1) for the information and guidance of Military Government health officials. This information which is also being disseminated by the Japan Medical Association and the Ministry of Welfare is designed to insure uniformity of methods and techniques to be followed in the selection and treatment of tuberculosis cases throughout Japan.

The article clearly indicates that there is still much to be learned about streptomycin particularly with respect to the types of cases in which it should be used as well as the proper dosage. However, the best available information is given and until further notice this article may be accepted as the official guide for the use of streptomycin in the treatment of tuberculosis in Japan. The great number of cases of tuberculosis in Japan as well as the acute shortage of proper isolation and treatment facilities has made it mandatory to introduce the drug before all the fine details concerning its effectiveness have been worked out.

1 Incl.

Streptomycin in the Treatment of Human Tuberculosis.



## STREPTOMYCIN IN THE TREATMENT OF HUMAN TUBERCULOSIS

The announcement of the discovery of streptomycin came at a time when the benefits of penicillin were becoming widely known. The lay press seized upon the articles by Feldman and Hinshaw (2,3,6) and soon led the world to believe that its tuberculosis problems were solved. In contrast with this is the confusion which still exists in professional literature.

Schatz, Bugie and Waksman (1) in January 1944 announced a "Streptomycin substance exhibiting anti-biotic activity against gram positive and gram negative bacteria." Feldman and Hinshaw's work followed. Since then many clinical observers (4,5,7,8,9,10,11,12,16,17,18,23,24) have reported. Most of these articles have concerned small groups of cases and generally the most dramatic forms of tuberculosis (meningeal, miliary, etc.) These cases were chosen because they offered their own control or end point (death) as a means of gauging success or failure. Since the pathology of these cases is very similar to that of artificially infected laboratory animals, it is not surprising that similar results can be obtained. When the therapy is given to other more chronic types of tuberculosis, the results are much harder to evaluate and much confusion as to the indications for use still persists. References are given to many of these articles but to abstract all of them would produce utter confusion.

In the United States individual investigators, the Veterans Administration, the Army and Navy, the United States Public Health Service, and the Therapy Committee of the American Trudeau Society (13,14,15,16) have, all together studied the effects of the drug in about 2,000 patients with results which suggest the following deductions:

- (1) Streptomycin should be tried in all cases of miliary tuberculosis, for more than half of such patients will be alive, and a substantial number of them will be free from clinical, X-ray, or laboratory signs of disease from 6 to 12 months after discontinuation of the drug.
- (2) The use of the drug in tuberculosis meningitis is mandatory, for about one fourth of all patients have survived from 6 to 12 months after treatment, and the majority of these are free from detectable signs of tuberculosis.
- (3) Acute tuberculous pneumonia or exudative (fresh) tuberculous disease of the lungs will usually show recession, with notable clearing of the lungs demonstrable roentgenographically within a few weeks. Tubercle bacilli disappear from the sputum in about half of these cases. Such patients, however, need still further sanatorium care.
- (4) Extrapulmonary tuberculosis is under detailed study, but already it appears that tuberculous laryngitis and bronchitis are benefited by the use of streptomycin in about 85 percent of cases, even though the parent



lesion in the lungs may show no improvement. Tuberculous enteritis and cystitis likewise tend to improve. In fact, in areas in which the disease affects the epithelial surfaces, results are generally good; cutaneous sinuses are benefited. However, tuberculosis of the osseous and genito-urinary systems needs further study.

(5) Streptomycin is used profitably at times to enhance the patient's chances from collapse therapy and as a prophylactic in surgical treatment, particularly pulmonary resection.

In the face of these relatively good results, however, the average case of fibrocavernous tuberculosis has been found as yet to respond poorly to streptomycin; this type represents three fourths of all cases of the disease. It is still under intensive study. Moreover, the toxicity of the drug and the development of streptomycin-fastness by M. Tuberculosis are disturbing factors.

In the early experience with this drug, with large doses of 2,3, or even 5 Gm. a day, toxic symptoms were very common. Even with a standard dose of 1.8 Gm., vertigo developed in approximately 92 percent of one large series of patients. McDermott, (II) among others, has pointed out the common indices of toxicity. Vestibular dysfunction predominates, characterized by vertigo, dizziness, headache, and nausea, some of which are present to some degree in almost all patients who take large doses. Vertigo occurs in 20 percent or more of those receiving 1.0 Gm. per day, which is now the prevailing dose. It may be permanent. Deafness, partial or complete, has been observed. It occurs rarely except when the drug is applied intrathecally for tuberculous meningitis or (less often) in persons with impaired renal function who receive large doses. Further damage to the kidneys may occur in this latter group, a fact which indicates the propriety of determining the condition of the urinary tract prior to administration of the drug. In patients with already lowered renal function, blood levels may become high and various toxic symptoms ensue. Other indications of toxicity are anaphylactic manifestations - fever, itching, dermatitis and eosinophilia - and agranulocytosis. The latter appears in less than 1 percent of cases and is usually an indication for prompt discontinuation of treatment.

The development of streptomycin resistance by M. tuberculosis, occurring rather regularly, presents a serious obstacle in the use of the drug. Whether this represents a biological adjustment to a new environment or the survival and increasing preponderance of natively resistant bacilli in the diseased body is not known. Once it becomes manifest, however, it appears to persist, and resistant strains have been maintained in culture for considerably over a year and have been passed through animals without reverting.

The production of resistant strains should be a serious consideration in the therapeutic use of streptomycin in patients manifestly



unlikely to recover because the spread of such strains could conceivably become a grave public health hazard. To obviate this, careful selection of cases and frequent invitro examination after the first 6 weeks of treatment are indicated, but continuation of the drug beyond 6 weeks is to be discouraged.

In general, streptomycin should be withheld in cases of minimal tuberculosis and in those in which conventional treatment offers reasonable prospect of good result. It provides an excellent medium of treatment for certain types of tuberculosis, but it should be used in association with accepted therapeutic measures and not as a substitute for them. A tendency is at present developing to use the drug only as an adjunct rather than as a definitive treatment in all types of tuberculosis except the miliary and meningitic forms, and to apply it briefly for three, four or six weeks at the utmost opportune time with other appropriate therapy."

The desirability of withholding streptomycin from cases in which there is doubt as to whether it would be effective is underlined by a report of Spendlove, Cummings, Fuchler and Michael (20) in which they describe the development of a streptomycin loving strain.

"A strain of *Mycobacterium tuberculosis*, growth of which is markedly enhanced by the presence of streptomycin in the culture medium has been isolated from the sputums of a patient who had received this antibiotic for the treatment of pulmonary tuberculosis. The patient's infection exhibited rapid progression during the course of streptomycin therapy."

The public health implications of this observation are obvious. For the individual it means that therapy should be reserved for periods during which it can reasonably be expected to be effective. (19,21,22).

The preceding has been condensed from the experience in a country where the tuberculosis rate is not high; where there are adequate treatment facilities and where the general nutrition of the people is good. Conditions are different in Japan and it is felt that the dangers from the use of the drug are far outweighed by the possible benefits. It is hoped that it will be used in all early cases as soon as possible after careful diagnosis.

At the present time only two methods of administration are in common use.

1. Intramuscular. Solutions are prepared in pyrogen free distilled water or physiological saline solution. These solutions may be stored at room temperature under aseptic conditions for one week without significant loss of potency. Solutions should not be autoclaved. Only clear solutions, free from dissolved particles should be used. Solutions should not have a streptomycin concentration greater than 250 mg. per cc. Injections are made intramuscularly into gluteal thigh or deltoid muscles in solution.



2. Intrathecal Injection. Effective concentrations in cerebrospinal fluid may be obtained only by intrathecal injection. Only clear solution, free from undissolved particles, should be used intrathecally. Inject solutions containing 50 to 200 mg., in 5 to 10 cc of sterile, pyrogen-free, physiologic saline solution. Concomitant intramuscular injections are necessary for effective blood concentration.

Summary - Indications for use of streptomycin in tuberculosis have not yet been fully determined.

At present it is considered that the optimum dosage is much lower than that previously employed.

A working schedule of indications is as follows:

1. Mandatory in the treatment of:
  - a. Tuberculous meningitis,
  - b. Acute hematogenous miliary tuberculosis - in both of which is advisable to begin streptomycin treatment as soon as the diagnosis is reasonably certain.
2. Indicated in the treatment of:
  - a. Tuberculosis laryngitis and ulcerating oropharyngeal lesions,
  - b. Tracheobronchial tuberculous ulcerations and granulations;
  - c. Tuberculous, draining cutaneous sinuses - other than those from underlying tuberculous empyema;
  - d. Tuberculous enteritis and tuberculous peritonitis;
  - e. Tuberculous pneumonia
  - f. Pulmonary tuberculosis, particularly where an exudative component is prominent.

(Note: At present, streptomycin is not advocated for general use in patients whose lesions are chronic fibroid or fibrocaseous, although it has proved beneficial in the treatment of recent bronchogenic spreads occurring in chronic fibrocavernous tuberculosis. Further, the consensus holds that streptomycin usually is of little value in those cases in which the lesions are acute, destructive, and apparently terminal, and in chronic empyemas of tuberculous origin.



- g. Chest surgery cases, as a pre- and post- operative measure.
- 3. Deserves additional trial in the treatment of:
  - a. Genitourinary tuberculosis.
  - b. Tuberculosis of the pericardium, bones, joints, skin and eyes;
  - c. Tuberculous lymphadenitis.

Recommended dosage: 1 gram a day for 40 days.  
The daily dose should be divided into two or more parts. In certain cases, this course may be repeated after a reasonable interval of time.



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